Attorney Docket No.: ISPH-0588
Inventors: -Crooke et al.
Serial No.: 09/918,026
Filing Date: July 30, 2001
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Please amend the claims as follows:

1. (twice amended) A compound 8 to 50 nucleobases in length targeted to a coding region of a nucleic acid molecule encoding human acyl-CoA cholesterol acetyltransferase-2 (SEQ ID NO: 3), wherein said compound specifically hybridizes with said region and inhibits the expression of human acyl-CoA cholesterol acetyltransferase-2.

REMARKS

Claims 1, 2 and 4-20 are pending in the instant application. Claims 15-20 have been withdrawn from consideration. Claims 1, 2 and 4-14 have been rejected. Claims 11 and 15-20 have been canceled. Claim 1 has been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Election/Restriction

The Restriction Requirement wherein Applicants elected with traverse Group I, claims 1, 2 and 4-14 has been deemed proper and therefore made Final. Accordingly, Applicants have canceled claims 15-20 without prejudice, with Applicants reserving the right to file continuing applications on the canceled subject matter.

II. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 4-14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Cases et al. (WO 99/67368) and Sturley (WO 97/45439), and further in view of Baracchini et al. (US Patent 5,801,154) and Fritz et al. (1997). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill to make antisense oligonucleotides as claimed because the art has asserted that acyl CoA cholesterol acetyltransferase is an enzyme involved in cholesterol esterification and absorption (Cases et al.). The Examiner suggests that one of skill would have been motivated since the art has taught the desirability of modified antisense oligonucleotides over native forms (Baracchini et al. and Fritz et al.), while an expectation of success is provided by the teaching of Cases et al. and Sturley et al. where they teach use of compounds that are antisense for inhibition of expression of the gene. Applicants respectfully traverse this rejection.

At the outset, Applicants have canceled claim 11 and amended the claims to list a specific region within human acyl CoA cholesterol acetyltransferase (SEQ ID NO: 3) that is targeted by antisense compounds. Support for this amendment to the claims can be found throughout the specification as filed but in particular at pages 86-88. Nowhere does the cited references teach or suggest

use of antisense compounds targeted to the coding region as now claimed.

Cases et al. (WO 99/67368) disclose nucleic acid molecules encoding acyl CoA cholesterol acetyltransferase 2, as well as polypeptides and uses of the nucleic acids in diagnostic applications and treatments. Although the application mentions the idea of using antisense compounds as a way to modulate activity of acyl CoA cholesterol acetyltransferase 2, nowhere does the application provide data showing successful inhibition of gene expression using antisense compounds as claimed in the instant specification. It is only with the specification in hand that one of skill understands how to specifically design antisense for use to inhibit expression of acyl CoA cholesterol acetyltransferase 2.

Sturley et al. (WO 97/45439) disclose nucleic acid molecules encoding acyl CoA cholesterol acetyltransferase-2 and their uses in patients to treat disease. Although the application mentions the idea of using antisense compounds as a way to modulate activity of acyl CoA cholesterol acetyltransferase 2, nowhere does the application provide data showing successful inhibition of gene expression using antisense compounds as claimed in the instant specification. It is only with the specification in hand that one

of skill understands how to specifically design antisense for use to inhibit expression of acyl CoA cholesterol acetyltransferase 2.

The secondary references cited fail to overcome the deficiencies in teaching of these primary references.

The '154 patent teaches modification to antisense oligonucleotides in general as a way to enhance activity. However, this general discussion of modified oligonucleotides does not teach or suggest use of antisense compounds of any type to target a specific region of the human acyl CoA cholesterol acetyltransferase 2 (SEQ ID NO: 3) and the successful inhibition of expression using antisense.

Fritz et al. (1997) discloses cationic polystyrene nanoparticles as carrier systems for antisense compounds in general. This paper, however, does not teach or suggest use of antisense compounds of any type to target the human acyl CoA cholesterol acetyltransferase 2 (SEQ ID NO: 3), or any region within the sequence of this nucleic acid molecule, and the successful inhibition of expression using antisense.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the

art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. The limitations of the claims as now amended, which specify a specific region within acyl CoA cholesterol acetyltransferase 2 (SEQ ID NO:3), are not taught or suggested by any of the references individually or when combined. Therefore, the limitations of the claims as amended clearly are not taught or suggested by the combination of prior art references, nor is any expectation of successful use of such antisense compounds provided by the combination of prior art. It is only with the specification in hand that one of skill would understand that a specific region of acyl CoA cholesterol acetyltransferase 2 could be targeted successfully with antisense compounds. Thus, the combination of prior art cited cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Respectfully submitted,

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Date: **February 19, 2003**

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 11 and 15-20 have been canceled.

Claim 1 has been amended as follows:

1. (twice amended) A compound 8 to 50 nucleobases in length targeted to a coding region of a nucleic acid molecule encoding human acyl-CoA cholesterol acetyltransferase-2 (SEQ ID NO: 3), wherein said compound specifically hybridizes with said region and inhibits the expression of ~~a nucleic acid molecule encoding~~ human acyl-CoA cholesterol acetyltransferase-2.